rejected under 35 U.S.C. §102 (b) as being anticipated by or in the alternative under §103 as being obvious over van Atta et al. US Patent No. 5,478,729 (Van Atta). Claim 1, 14-16, 19, 21-30, 32, 33, 37-44 and 46 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of Van Atta.

Applicants believe that the amendments to and remarks regarding the claims overcome the rejections.

§112, Second Paragraph Rejections

A. Regarding claims 32 and 44, the Examiner states that "ligand" and "receptors" should state "antibody" in the light of the definition of "immunocomplex". The claims have been amended to recite "antibody".

B. Regarding claims 1, 19, 32 and 44, the Examiner states "a protected alkylating agent" is indefinite as to what portion of the alkylating agent is being protected and from what chemical conditions and/or reaction protection is being sought. Applicants respectfully traverse the rejection. The term "protecting" is clearly defined in the Specification. See for instance page 17, lines 15-25 and page 19, lines 20-25. Furthermore, several examples are listed. A protected alkylating agent has a functional group that when unprotected would react with a nucleophilic group. However, to further prosecution, Applicants have amended the claims to more particularly point out and distinctly claim the subject matter.

C. The Examiner states that "the reagent" lacks clear antecedent basis in claims 1, 15 and 16. Applicants have deleted the phrase containing the term in claim 1 and have amended the term in claims 15 and 16 to recite "composition".

D. Regarding claims 15, 19, 32, 44 and 46, the Examiner states that the term "chemically modifying homocysteine" or "homocysteine is modified by a reagent" lacks metes and

bounds regarding the type of homocysteine modifications within the scope of the claim and the resulting structure. Applicants do not believe the term is in claim 15 and ask that the Examiner clarify. In claims 19 as amended, the claim states that the protected functional group when unprotected reacts with a nucleophilic group on homocysteine to form a modified homocysteine. Thus, Applicants submit that the claim has the metes and bounds of the type of modification and the resulting structure. Further in claims 32 and 44 the protected functional group when unprotected reacts with the sulfhydryl group of homocysteine thus determining the metes and bounds of the type of modification and resulting structure. Claim 46 has been cancelled.

Applicants submit that the amendments and remarks overcome the rejections under 35 U.S.C. §112, second paragraph and ask that the Examiner withdraw the rejections.

§102(b,e) Rejections under Metzger

Claims 1 and 14 were rejected as being anticipated by Metzger. With respect to claim 1, the Examiner states that Metzer discloses a "protected alkylating agent" of formula III (col. 2, line 45) and with respect to claim 14, that Metzger also discloses a "disulfide reducing agent" (e.g. ZN in HCL/H2SO4). The Examiner gives no patentable weight to "deprotection of said reagent is catalyzed by an enzyme".

With respect to claim 1, Formula III of Metzger does not contain a protected functional group which is unreactive to a nucleophilic group when in the presence of a nucleophilic group. To the contrary and as is shown by Metzger, Formula III when in the presence of a nucleophilic group reacts with the nucleophilic group. It is unprotected. For instance, in Formula II a nucleophilic group (a sulfhydryl) will form upon contact with a strong reducing agent such as the Zn/acid mixture. Upon forming the nucleophilic group from the compound of Formula II, the nucleophilic group reacts with the compound in Formula III to

form the compound in Formula I. In complete contrast, substituting the composition of claim 1 for Formula III there would be no reaction with a nucleophilic group generated from Formula II from the action of the Zn/acid mixture because the compositions of claim 1 comprise an alkylating agent that comprises a "protected functional group" not found, disclosed, or even suggested by Metzger.

The same applies to claim 14. Even in the presence of a reducing agent such as the Zn/acid mixture the "protected functional group" remains protected. This is neither taught nor suggested by Metzger.

Thus, Applicants urge that the Examiner withdraw the rejection.

102(b) Rejections under Van Atta

Claims 1, 14-16, 19, 21-30, 32, 33, 27-44 and 46 stand rejected as being anticipated by Van Atta. Claim 46 has been cancelled.

The Examiner states that Van Atta discloses compositions, kits and assays for performing immunodetection of homocysteine - both homogeneous and heterogeneous and that Van Atta discloses "modifying reagents, especially "alkylating reagents' and preferentially BABA. The examiner states that BABA (e.g. example IV) and a modified BABA (e.g. BABA-N-hydroxysuccinamide ester at col. 21) are "protected alkylating agents" within the scope of the claimed invention. In addition the Examiner states that Van Atta also discloses "releasing agents" particularly "disulfide reducing agents". Thus, the Examiner concludes that claims 1 and 14-16 which merely require a "protected alkylating reagent alone or further combined with a disulfide reducing agent" (e.g. TCEP). Applicants respectfully traverse the rejection.

Applicants claim a "protected alkylating reagent", that is as currently recited: a composition comprising an alkylating reagent having a protected functional group_ which is unreactive to a nucleophilic group when in the presence of a nucleophilic group. Van Atta does not disclose an alkylating reagent that has

a protected functional group wherein the protected functional group is unreactive to a nucleophilic group when in the presence of a nucleophilic group. Van Atta instead discloses the opposite. With reference to BABA: When BABA is in the presence of a nucleophilic group (e.g. reduced homocysteine) the BABA reacts with the free Hcy. See Van Atta at column 29, lines 60 to column 30, lines 35. Thus, BABA is not a "protected alkylating reagent. It is not unreactive to a nucleophilic group when in the presence of such nucleophilic group. The same holds true for BABA-NHS. Van Atta at column 22, line 15 describes the reaction of BABA-NHS with BSA, which in the presence of DMSO forms BABA-activated BSA. In turn the BABA-activated BSA reacts with homocysteine. See column 22, lines 14-59. In contrast, a protected-BABA would not react with a nucleophilic group until the protected functional group was deprotected. Thus, Van Atta does not disclose or suggest the present invention. Further, Applicants note that the use of alkaline phosphatase as discussed in Van Atta at col. 21-23 and throughout Van Atta has nothing to do with using alkaline phosphatase to "deprotect" a "protected" alkylating reagent as claimed by Applicants. Van Atta does not disclose alkylating reagents that have a protected functional group capable of reacting with a nucleophilic group when deprotected wherein the protected functional group is unreactive to a nucleophilic group when in the presence of a nucleophilic group. There is nothing the alkylating reagents disclosed in Van Atta that could be "deprotected" by alkaline phosphatase. Thus, Applicants respectfully request that the rejections under Van Atta be likewise withdrawn.

Nonstatutory Double Patenting Rejections under Van Atta

Claims 1, 14-16, 19, 21-30, 32, 33, 27-44 and 46 stand rejected under the judicially created doctrine of double patenting over claims 1-29 of U.S. 5,478,729 (Van Atta). Applicants note that claim 46 has been cancelled.

Applicants submit that the claims are not obvious in view of Van Atta for the reasons discussed above. Van Atta neither

discloses nor suggests the protected alkylating reagents defined by the claims as amended. In contrast to the present invention the alkylating reagents disclosed by Van Atta react with nucleophilic groups. Thus, Applicants respectfully request that the rejection be withdrawn.

If the Examiner believes that a telephone call to the undersigned would clarify any issue, Applicants respectfully invite the Examiner to contact Applicants attorney at the phone number given below.

Respectfully submitted,

Cynthia G. Tymeson
Registration No. 34,745
Attorney for Applicants

Dade Behring Inc.
1717 Deerfield Rd.
Deerfield, Illinois 60015
Phone Contact: 847-267-5365 (or 5367)
Fax Contact: 847-267-5376